UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,551	12/11/2001	Keith D. Allen	R-227	4290

7590 03/25/2004

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,551	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 12/22/03 has been entered.

New claims 33-46 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

New claims 33-46 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is **specific and substantial,** or a well established utility, partially for the reasons already set forth in the previous Office Action mailed on 6/17/2003 (pages 3-5) and for the following new ground of rejection necessitated by Applicants' amendment.

The invention is drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a transgenic mouse whose genome comprises a disruption (both homozygous and heterozygous disruption) in the BSMAP gene as well as a cell or tissue obtained from the same transgenic mouse, a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

The specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, wherein the transgenic mouse displays **supposedly a significantly increased Prepulsed inhibition**, particularly with a 100 dB prepulse in comparison with the age- and gender matched wild-type control mouse (page 51, lines 29-31). However, upon examination of Figure 3, the only relevant data provided by the instant specification, the observed difference in Prepulsed inhibition between the transgenic mouse comprising a homozygous disruption of the BSMAP gene and the wild-type control mouse is apparently not statistically significant (please note that the error bars of the Prepulse inhibition values for the control wild-type mouse extend to and include the mean Prepulse inhibition values for the transgenic knockout mouse). Therefore, there is no apparent significant difference or obvious difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption of the BSMAP gene. It is noted that the Prepulse inhibition (PPI) test only reflects one component of the startle reflex response. Moreover, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2), all of which clearly indicate that the homozygous mutant mouse of the instant invention appears to be not an acceptable model of schizophrenia. Furthermore, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including

schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002), and that even in 2002 there is still no gene or genes that have been confirmed as "schizophrenia genes". Therefore, how can any agent modulating a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of schizophrenia?

At the effective filing date of the present application, little was known about the physiological role or function of the BSMAP gene. Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). Because the defined function for the BSMAP or its gene is not known and is not taught in the specification, the invention has no utility which is **specific** and **substantial** at the effective filing date of the present application. The speculation that BSMAP may play a generic role in brain function or its gene disruption is somehow associated with schizophrenia is not deemed to be a specific and substantial utility for the presently claimed invention.

The specification asserts a variety of utilities for the claimed invention, including uses of the cell-and animal-based systems of the present invention as models for diseases, for identifying compounds that ameliorate disease symptoms, for production

of antibodies, for identifying agents that modulate the expression or the function of the BSMAP gene. However, such uses would require the determination of the physiological function or role of the BSMAP gene and its gene product, and in the absence of such guidance provided by the instant specification and in the prior art, they do not constitute a substantial utility at the effective filing date of the present application. A substantial utility is a utility that defines a "real world" use. Utilities which require further research to identify or confirm a real world use are not substantial utilities.

For the reasons set forth above, a skilled artisan would not be able to use the presently claimed invention for any substantial purpose without further research and experimentation.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed 12/22/03 (pages 5-6) have been fully considered, but they are not found persuasive.

Applicant asserts that Applicant clearly disclosed in the instant application that a statistically significant difference was observed between the transgenic mouse and wild type mice. Applicant further argues that the presence of overlapping error bars does not necessarily establish or support a lack of statistical significance as asserted by Examiner. Applicant also argues that with respect to the new set of claims, prepulse inhibition, at the time of filing, was known in the art and taught by the instant specification to be associated with schizophrenia. Therefore, the transgenic mouse as claimed would be supported by a variety of utilities, such as, for example, the

investigation into and/or discovery of therapeutic agents related to schizophrenia or as an animal model related to schizophrenia.

Firstly, common sense would dictate that there is no apparent statistically significant difference between the PPI values observed after a 100 decibel prepulse for the homozygous mutant mouse and a wild-type mouse in Figure 3. The range of PPI values for both the homozygous mutant mouse and a wild-type mouse is overlapped as shown in Figure 3. This factual evidence is opposite to Applicant's assertion that there is a statistically significant difference in PPI responses observed between the transgenic mouse and wild type mice. Therefore, on the basis of the data presented in this application, it is reasonable to conclude that there is no significant difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption of the BSMAP gene.

Secondly, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002). Additionally, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2). Moreover, there is still no gene or genes that have been confirmed as "schizophrenia genes" in 2002, let alone at the effective filing date of the present application (Geyer et al., Mol. Psychiatry 7:1039-

1053, 2002). Furthermore, nothing was known about the physiological role or function of the BSMAP gene, and that Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) also state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19" (page 55, col. 2, second last sentence) in reference to the location of human BSMAP on human chromosome 19p12. Thus, at the effective filing date of the present application it is not clear what is the significance of the data reported in Figure 3, and that the homozygous transgenic mouse of the present invention has anything to do with schizophrenia.

Accordingly, the speculation that BSMAP may play a generic role in brain function or its gene disruption is somehow associated with schizophrenia is not deemed to be a specific and substantial utility for the presently claimed invention. Therefore, new claims 33-46 are rejected under 35 U.S.C. 101 for the reasons set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claims 33-46 are rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35 U.S.C. 101, one skilled in the art would not know how to use the claimed invention at the effective filing date of the present application.

The specification is not enabled for the present claimed invention in part for the same reasons already set forth in the previous Office Action mailed on 6/17/03 (pages 6-10), and for the following reasons directly to the new claims.

(1) The breadth of the claims. The instant claims are drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a transgenic mouse whose genome comprises a disruption (both homozygous and heterozygous disruption) in the BSMAP gene as well as a cell or tissue obtained from the same transgenic mouse, a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). In effect, little was known about the physiological role or function for BSMAP gene and its gene product. Additionally, even several years after the effective filing date of the present application (12/13/2000), there is still no gene or genes that have been confirmed as "schizophrenia

genes". Furthermore, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002).

(3) The amount of direction or guidance provided. Apart from the disclosure of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting an increased Prepulsed inhibition with a 100 dB prepulse that is not statistically significant (see Figure 3) in comparison with the age- and gender matched wild-type control mouse, the specification fails to provide sufficient guidance for a skilled artisan on how to use such homozygous mutant mice. On the basis of the instant disclosure, it is not clear what is the significance of the non-statistical difference in the PPI responses observed for the homozygous mutant mouse and a wild type mouse. It is noted that the Prepulse inhibition test only reflects one component of the startle reflex, and it is not a representative test for evaluating stimulus processing abnormality in general. While it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002). Additionally, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2). Moreover, there is still no gene

or genes that have been confirmed as "schizophrenia genes" in 2002, let alone at the effective filing date of the present application; and that nothing was known about the physiological role or function of the BSMAP gene or any genetic disease has been mapped to locus of the BSMAP gene (Elson et al.; Biochem. Biophys. Res. Commun. 264:55-62, 1999). Therefore, how can any agent modulating a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of schizophrenia?

It is also unclear on the basis of the present disclosure, how can one **use** a transgenic mouse comprising a heterologous disruption of the BSMAP gene without any phenotype distinguishable from a wild-type mouse? Similarly, it is unclear how cells obtained from any transgenic mouse of the presently claimed invention that do not possess any phenotype can be used and for what purposes. As enablement requires the specification to teach how to make and **use** the claimed invention, given the lack of sufficient guidance provided by the present application and in light of the state of the relevant prior art as discussed above, it would have required undue experimentation for a skilled artisan to make and **use** the instant claims.

Response to Arguments

Applicant's arguments related to the above rejection in the Amendment filed 12/22/03 (pages 7-8) have been fully considered, but they are not found persuasive.

Applicant relies on the same arguments in response to the utility rejection under 35 U.S.C. 101 for overcoming the rejection under 35 U.S.C. 112, First Paragraph. With

respect to the new set of claims, Applicant asserts that one skilled in the art would be able to make and use the presently claimed invention.

Applicant's arguments in response to the utility rejection are not found persuasive for the reasons already set forth in the above Response to Arguments. Additionally, Examiner maintains that based on the analysis of the Wands factors already discussed at length above, an ordinary skilled artisan would still not know how **to use** the presently claimed invention.

Therefore, new claims 33-46 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new ground of rejection necessitated by Applicants' amendment.**

Claim 46 is indefinite because there is no connection between the step of determining whether the potential therapeutic agent modulates prepulse inhibition in the transgenic mouse with modulation of seizure susceptibility. Is there a separate step for determining seizure susceptibility? As written, the metes and bounds of the claim are not clearly determined.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER